Claims

1. A process for producing an optically active 3-(4-hydroxyphenyl)propionic acid of the formula (6):

$$\begin{array}{c|c}
R^{5} & *C00H \\
H0 & R^{8} & 0R^{2}
\end{array}$$
(6)

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wherein R^2 is an alkyl group, R^5 to R^8 are each independently a hydrogen atom or a substituent; and the symbol * is a chiral carbon atom,

or a salt thereof, which comprises reacting a benzaldehyde of the formula (1):

$$R^5$$
 R^6
 CHO
 R^1O
 R^8
 R^8

wherein R^1 is a protective group; and R^5 to R^8 are each the same as defined above,

with a glycolic acid derivative of the formula (2):

$$R^2O$$
 $COOR^3$ (2)

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wherein ${\ensuremath{R}}^3$ is a hydrocarbon group, and ${\ensuremath{R}}^2$ is the same as defined above,

hydrolyzing the resulting product to give a cinnamic acid of the formula (4):

$$\begin{array}{c|c}
R^5 & C00H \\
R^10 & R^8 & 0R^2
\end{array}$$
(4)

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wherein R^1 , R^2 , and R^5 to R^8 are each the same as defined above, or a salt thereof, and subjecting the cinnamic acid (4) or a salt thereof to asymmetric hydrogenation to give an optically active phenylpropionic acid of the formula (5):

$$\begin{array}{c|c}
R^5 & *C00H \\
R^10 & R^8 & 0R^2
\end{array}$$
(5)

wherein all the symbols are each the same as defined above, or a salt thereof, followed by deprotection.

2. A process for producing an optically active 3-(4-hydroxyphenyl) propionic acid of the formula (6):

$$R^{5}$$
 R^{6}
 R^{6}
 R^{8}
 R^{8}
 R^{8}
 R^{7}
 R^{8}
 R^{8}
 R^{8}
 R^{8}

wherein R^2 is an alkyl group; R^5 to R^8 are each independently a hydrogen atom or a substituent; and the symbol * is a chiral carbon atom,

or a salt thereof, which comprises reacting a benzaldehyde of the formula (1):

$$R^{5}$$
 R^{1}
 R^{1}
 R^{1}
 R^{1}
 R^{2}
 R^{3}
 R^{1}
 R^{2}
 R^{3}
 R^{4}

wherein R^1 is a protective group; and R^5 to R^8 are each the same as defined above,

with a glycolic acid derivative of the formula (2):

$$R^2O$$
 $COOR^3$ (2)

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wherein R^3 is a hydrocarbon group, and R^2 is the same as defined above, followed by hydrolysis to give a cinnamic acid of the formula (4):

- wherein R^1 , R^2 , and R^5 to R^8 are each the same as defined above, or a salt thereof, and subjecting the cinnamic acid (4) or a salt thereof to asymmetric hydrogenation.
- 3. A process for producing an optically active 3-(4-15 hydroxyphenyl)propionic acid of the formula (6):

$$R^{5}$$
 R^{6}
 R^{8}
 R^{8}
 R^{8}
 R^{8}
 R^{7}
 R^{8}
 R^{8}

wherein R^2 is an alkyl group; R^5 to R^8 are each independently a hydrogen atom or a substituent; and the symbol * is a chiral carbon atom,

or a salt thereof, which comprises reacting a 4-hydroxybenzaldehyde of the formula (7):

$$R^5$$
 R^6
 CHO
 R^8
 R^8

wherein R^5 to R^8 are each the same as defined above, with a glycolic acid derivative of the formula (2):

$$R^2O$$
 $COOR^3$ (2)

wherein R³ is a hydrocarbon group; and R² is the same as defined above, followed by hydrolysis to give a 4-hydroxycinnamic acid of the formula (9):

$$R^{5}$$
 R^{6}
 R^{8}
 R^{8}
 R^{2}
 R^{8}
 R^{8}
 R^{8}
 R^{8}
 R^{8}

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wherein R^2 , and R^5 to R^8 are each the same as defined above, or a salt thereof, and subjecting the 4-hydroxycinnamic acid (9) or a salt thereof to asymmetric hydrogenation.

4. The process according to any one of claims 1 to 3, wherein the asymmetric hydrogenation is carried out in the presence of a chiral catalyst.

- 5. The process according to any one of claims 1 to 4, wherein the chiral catalyst is a transition metal complex.
- 6. The process according to claim 5, wherein the transition metal complex is a complex of the metal of Groups 8 to 10 in the periodic table.
- 7. A process for producing an optically active 10 carboxylic acid of the formula (12):

$$R^{12}$$
 $*$
 $COOR^{13}$
 OR^{14}
(12)

wherein R^{11} and R^{12} are each independently a hydrogen atom or a substituent; R^{13} is a hydrogen atom, an optionally substituted hydrocarbon group or a metal atom; R^{14} is a hydrogen atom or a protective group; and the symbol * is an chiral carbon atom, or a salt thereof, which comprises subjecting an α,β -unsaturated carboxylic acid of the formula (11):

$$R^{12}$$
 $COOR^{13}$
 OR^{14}
(11)

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wherein R¹¹ to R¹⁴ are each the same as defined above,

or a salt thereof, to asymmetric hydrogenation in the presence
of a transition metal complex, provided that when the transition
metal complex is rhodium, the protective group represented by
R¹⁴ in the above formula (11) is a group other than acyl.

8. The process according to claim 7, wherein the transition metal complex is a complex of the metal of Groups 8 to 10 in the periodic table.

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- 9. The process according to claim 1 or 3, wherein the chiral catalyst is a mixture of a chiral ligand and a transition metal compound.
- 10. The process according to any one of claims 1 to 3, wherein the optically active phenylpropionic acid of the formula (5) or a salt thereof obtained by the method according to any one of claims 1 to 3 is crystallized from a solvent.
- 11. The process according to claim 10, wherein the solvent used for the crystallization is a member selected from the group consisting of hydrocarbons, alcohols, ketones and water, and a mixture thereof.
- 20 12. The process according to any one of claims 1 to 3, wherein the optically active 3-(4-hydroxyphenyl)propionic acid of the formula (6) or a salt thereof obtained by the method according to any one of claims 1 to 3 is crystallized from a solvent.

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13. The process according to claim 12, wherein the solvent used for the crystallization is a member selected from the group consisting of aromatic hydrocarbons, aliphatic hydrocarbons, alcohols and water, and a mixture thereof.

14. A process for producing an optically active phenylpropionic acid of the formula (5):

$$\begin{array}{c|c}
R^{5} & *C00H \\
R^{1}O & R^{8} & OR^{2}
\end{array}$$
(5)

wherein R¹ is a protective group; R² is an alkyl group; R⁵ to R⁸ are each independently a hydrogen atom or a substituent; and the symbol * is an chiral carbon atom,

or a salt thereof

which comprises subjecting a cinnamic acid of the formula (4):

$$\begin{array}{c|c}
R^5 & COOH \\
R^1O & R^8 & OR^2
\end{array}$$
(4)

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wherein R^1 , R^2 , and R^5 to R^8 are each the same as defined above, or a salt thereof,

to asymmetric hydrogenation.

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15. A process for producing an optically active 3-(4-hydroxyphenyl)propionic acid of the formula (6):

$$\begin{array}{c|c}
R^5 & *COOH \\
\hline
HO & R^8 & OR^2
\end{array}$$
(6)

wherein R^2 is an alkyl group; R^5 to R^8 are each independently a hydrogen atom or a substituent; and the symbol * is a chiral carbon atom,

or a salt thereof, which comprises subjecting a cinnamic acid of the formula (4):

$$\begin{array}{c}
R^{5} \\
R^{1}O
\end{array}$$

$$\begin{array}{c}
R^{8} \\
R^{7}
\end{array}$$

$$\begin{array}{c}
R^{8} \\
R^{8}
\end{array}$$

$$\begin{array}{c}
R^{2} \\
R^{3}
\end{array}$$

$$\begin{array}{c}
R^{4}
\end{array}$$

wherein R^1 , R^2 , and R^5 to R^8 are each the same as defined above, or a salt thereof, to asymmetric hydrogenation.

16. A process for producing an optically active 3-(4-hydroxyphenyl) propionic acid of the formula (6):

$$R^{5}$$
 R^{6}
 R^{8}
 R^{8}
 R^{2}
 R^{7}
 R^{8}
 R^{8}
 R^{2}
 R^{6}
 R^{6}
 R^{6}
 R^{6}
 R^{6}
 R^{6}
 R^{6}
 R^{6}
 R^{6}

wherein R^2 is an alkyl group; R^5 to R^8 are each independently a hydrogen atom or a substituent; and the symbol * is a chiral carbon atom,

or a salt thereof,

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which comprises subjecting a 4-hydroxycinnamic acid of the formula (9):

$$R^{5}$$
 R^{6}
 R^{8}
 R^{8}
 R^{8}
 R^{8}
 R^{8}
 R^{8}
 R^{8}
 R^{8}

wherein R^2 , and R^5 to R^8 are each the same as defined above, or a salt thereof to asymmetric hydrogenation.

17. A process for producing an optically active 3-(4-hydroxyphenyl)propionic acid of the formula (6):

$$\begin{array}{c|c}
R^5 & *C00H \\
H0 & R^8 & 0R^2
\end{array}$$
(6)

10

wherein R^2 is an alkyl group; R^5 to R^8 are each independently a hydrogen atom or a substituent; and the symbol * is a chiral carbon atom,

or a salt thereof, and an optically active phenylpropionic acid of the formula (5):

wherein R^1 is a protective group; and R^2 , R^5 to R^8 and the symbol * are each the same as defined above,

or a salt thereof, which comprises subjecting a cinnamic acid of the formula (4):

$$\begin{array}{c|c}
R^5 \\
\hline
R^10 \\
\hline
R^7
\end{array}$$

$$\begin{array}{c}
R^6 \\
\hline
R^8 \\
\hline
R^2
\end{array}$$

$$\begin{array}{c}
C00H \\
\hline
R^8
\end{array}$$

$$\begin{array}{c}
(4)
\end{array}$$

wherein R^1 , R^2 , and R^5 to R^8 are each the same as defined above, or a salt thereof, to asymmetric hydrogenation.

18. A process for producing an optically active 3-(4-hydroxyphenyl)propionic acid of the formula (6):

$$\begin{array}{c|c}
R^5 & * COOH \\
HO & R^8 & OR^2
\end{array}$$
(6)

wherein R^2 is an alkyl group, R^5 to R^8 are each independently a hydrogen atom or a substituent; and the symbol * is a chiral carbon atom,

or a salt thereof, which comprises reacting a benzaldehyde of the formula (1):

$$R^{5}$$
 R^{6}
 R^{1}
 R^{1}
 R^{8}
 R^{8}
 R^{8}

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wherein R^1 is a protective group; and R^5 to R^8 are each the same as defined above,

with a glycolic acid derivative of the formula (2):

$$R^2O$$
 $COOR^3$ (2)

wherein $\ensuremath{\mbox{R}}^3$ is a hydrocarbon group, and $\ensuremath{\mbox{R}}^2$ is the same as defined above,

hydrolyzing the resulting product to give a cinnamic acid of the formula (4):

$$\begin{array}{c|c}
R^5 \\
\hline
R^10 \\
\hline
R^7
\end{array}$$
COOH
$$\begin{array}{c}
R^8 \\
\hline
R^8
\end{array}$$
(4)

wherein R^1 , R^2 , and R^5 to R^8 are each the same as defined above, or a salt thereof, and subjecting the cinnamic acid (4) or a salt thereof to asymmetric hydrogenation to give an optically active phenylpropionic acid of the formula (5):

$$\begin{array}{c|c}
R^5 & *COOH \\
R^1O & R^8 & OR^2
\end{array} (5)$$

wherein all the symbols are each the same as defined above, or a salt thereof, and an optically active 3-(4-hydroxyphenyl)propionic acid of the formula (6):

$$R^{5}$$
 R^{6}
 R^{6}
 R^{8}
 R^{2}
 R^{8}
 R^{7}
 R^{8}
 R^{8}
 R^{8}
 R^{8}
 R^{8}

wherein all the symbols are each the same as defined above, or a salt thereof, followed by deprotection.

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Abstract

The present invention relates to a process for producing an optically active 3-(4-hydroxyphenyl)propionic acid useful as intermediates for medicines, through short steps in good yield and with high optical purity. More specifically, the present invention relates to a process for producing an optically active 3-(4-hydroxyphenyl)propionic acid of the formula (6):

$$\begin{array}{c|c}
R^5 & *C00H \\
\hline
 H0 & R^8 & 0R^2
\end{array}$$
(6)

10

5

wherein R^2 is an alkyl group; R^5 to R^8 are each independently a hydrogen atom or a substituent; and the symbol * is an chiral carbon atom,

or a salt thereof, which comprises reacting a benzaldehyde of the formula (1):

$$R^{5}$$
 R^{6}
 R^{1}
 R^{1}
 R^{8}
 R^{8}
 R^{8}

wherein R^1 is a protective group; and R^5 to R^8 are each the same as defined above,

with a glycolic acid derivative of the formula (2):

$$R^2O$$
 $COOR^3$ (2)

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wherein R³ is a hydrocarbon group; and R² is the same as defined

above,

hydrolyzing the resulting product to give a cinnamic acid of the formula (4):

$$\begin{array}{c|c}
R^5 \\
\hline
R^10 \\
\hline
R^7
\end{array}$$
COOH
$$\begin{array}{c}
R^8 \\
\hline
R^8
\end{array}$$
(4)

wherein R¹, R² and R⁵ to R⁸ are each the same as defined above, or a salt thereof, and subjecting the resulting cinnamic acid (4) or a salt thereof to asymmetric hydrogenation to give an optically active phenylpropionic acid of the formula (5):

wherein all the symbols are each the same as defined above, or a salt thereof, followed by deprotection.